REMARKS/ARGUMENTS

Claims 1-8, 10-12, and 17 are pending in the Application. Claim 17 has been withdrawn from further consideration by the Examiner as directed to an invention nonelected in response to a restriction requirement. No claim is currently amended.

Applicant appreciates the Examiner's withdrawal of the previous rejections of claims under 35 U.S.C. 112, 2nd ¶, and under 35 U.S.C. 103 over Ulmius (U.S. Patent 5,643,602, issued July 1, 1997). Office Action dated August 19, 2009 (OA), pages 3, 2nd ¶, and pages 4 and 7.

Rejections of Claims 1-8 and 10-12 under 35 U.S.C. 103 over Beckert

Previously presented Claims 1-8 and 10-12 stand finally rejected under 35 U.S.C. 103 over WO 01/68058, published September 20, 2001. The Examiner cites to, and relies upon, Beckert (U.S. Patent 6,632,454 B2, issued October 14, 2003) as the English language equivalent WO 01/68058. So shall we.

The claimed pharmaceutical formulation comprises:

a) an inner layer including budesonide bound in a binder, "wherein the binder is a polymer or copolymer with acidic groups,"

b) an intermediate layer, and

c) an outer envelope.

The inner layer of the claimed formulation must release the bound budesonide "to the extent of more than 80% after 30 min." in accordance with the release test specified in Claim 1.

At page 16, lines 10-17, Applicant's Specification teaches:

> A difference from WO 01/68058 is according to the invention that the inner layer a) is applied to the core which comprises the active ingredient budesonide bound in a polymeric binder with acidic groups. The increased budesonide solubility which is achieved in this way results in an even more advantageous embodiment.

Applicant recognized (Spec., p. 2, ll. 33-34), "One problem with pharmaceutical formulations containing the active ingredient budesonide is the low solubility of the active ingredient."

Prior art efforts to improve the solubility of budesonide added water-soluble excipients to the formulation (Spec., p. 2, ll. 35-37).

The Examiner rejected Applicant's claims over Beckert (WO 01/68058) because Beckert describes a pharmaceutical formulation comprising: a) an active agent core which may be budesonide and may be bound to a binder, b) an intermediate layer component Applicant claims (e.g., a copolymer of (meth)acrylic acid and (meth)acrylic acid ester including a quaternary ammonium group), and c) an outer envelope Applicant claims (e.g., a copolymer of (meth)acrylic acid and (meth)acrylic acid ester including an anionic group)(OA, pp. 3-4, bridging ¶). Applicant's Specification recognized and acknowledged Beckert's teaching (Spec., p. 2, ll. 8-29; p. 16, ll. 10-17). Applicant's Specification also acknowledged an art-recognized solubility problems associated with using budesonide as the active ingredient in multi-layer formulations (Spec., p. 2, ll. 33-37; p. 16, ll. 10-17).

However, in reference to Beckert's disclosure, the Examiner additionally found (OA, p. 4):

> The active substance can be budesonide. The dosage form includes a binder such as collidon 25 as well as an internal coat of Eudragit RS and RL [corresponding to Applicant's claimed intermediate layer] and an external enteric coating of Eudragit FS (Example 1 - pages 16-18)[corresponding to Applicant's claimed outer envelope].

Based on that evidence alone, the Examiner concludes, "The instant invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, given the teachings of Beckert."

Beckert teaches that its core may contain 1-95% active ingredient and pharmaceutical excipients (Beckert, col. 3, ll. 11-13 and 20-21). The core may also contain (Beckert, col. 3, ll. 20-25):

> . . . binders such as lactose, cellulose and derivatives thereof, polyvinylpyrrolidone (PVP), humectants, disintegration promoters, lubricants, disintegrants, starch and derivatives thereof, sugar solubilizers or others.

None of the specifically named binders is a "polymer or copolymer with acidic groups" as required in Applicant's current Claim 1. Beckert's examples describe active-ingredient-containing cores produced by a powder layering process (Beckert, col. 7, ll. 44-45). The cores were sprayed with the binder in a fluidized bed apparatus (Beckert, col. 7, ll. 65-67). Beckert's example recites "Kollidon 25" as the binder (Beckert, col. 7, ll. 59-61).

However, the Examiner agrees with Applicant that Kollidon 25 is a polyvinylpyrrolidone (PVP)(OA, p. 6). The Examiner also agrees with Applicant that Kollidon 25 is not an anionic polymer (OA, p. 6). Thus, the Examiner appears to agree with Applicant that no core binder described in Beckert is a "polymer or copolymer with acidic groups" as required in Applicant's current Claim 1. Moreover, Beckert does not suggest that the binder for the active ingredient may be a "polymer or copolymer with acidic groups". To the contrary, the BASF Technical Information brochure dated January 2004, entitled "Soluble Kollidon® grades" (of record), teaches that Kollidon® 25 is a PVP. While Applicant's own Specification teaches that Kollidon® VA64 is a polyvinylpyrrolidone/vinyl acetate copolymer with acidic groups which is suitable for use as the budesonide binder and dependent Claim 3 is specifically directed thereto, the Kollidon® 25 binder described in Beckert is not a PVP "polymer or copolymer with acidic groups" and the record does not suggest that Kollidon® 25 is a binder which is capable of releasing bound budesonide "to the extent of more than 80% after 30 min." in accordance with the release test specified in current Claim 1.

In response, the Examiner argues (OA, p. 6; emphasis added):

> However, the teachings of the prior art are not limited to the examples disclosed therein. The reference as a whole must be taken into consideration. In this instance, the prior art is well aware of <u>combining a binder component</u> with the active agent (budesonide) and is well aware of <u>providing a structured formulation</u> as is presently claimed herein.

With all due respect, there is no teaching in Becker to employ a "polymer or copolymer with acidic groups" as the binder for budesonide or any other active agent. Moreover, the Examiner erred in concluding that Applicant's claims do not recite the improved solubility, i.e., the solution to the solubility problems associated with budesonide bound to polymer or copolymer with acidic groups. Claim 1 requires that "the formulation of the inner layer without intermediate and outer layer releases the bound active ingredient in the release test according to USP XXIII monograph <711> "Dissolution" with apparatus 2 (paddle) with 100 revolutions/min in phosphate buffer of pH 7.5 to the extent of more than 80% after 30 min." On the other hand, Beckert's Figure 1 shows less than 80% release of active ingredient from uncoated pellets after 1 hour at a pH of 7.0. From that comparative evidence, it would appear to any person having ordinary skill in the art that the solubility and release of a low solubility active ingredient such as budesonide is much improved when the binder for the active ingredient is a polymer or copolymer with acidic groups as is required by Applicant's current claims. Beckert's Figure 1 shows less than 80% release of a representative active ingredient from uncoated pellets after 1 hour at a pH of 7.0. Applicant's claims require release of more than 80% of comparatively insoluble budesonide from the inner layer at a pH of 7.5 after 30 minutes.

The Examiner will recall that Applicant's Specification expressly states that budesonide is recognized in the art as an active agent with comparatively low solubility (Spec., p. 2, ll. 33-35; p. 16, ll. 10-17). The active agent in Applicant's current claims is limited to budesonide. Example 1 on pages 27-28 of the Specification shows that budesonide without binder has a very low release rate in water buffered to a pH of 7.5 after 1 hour. The release rate shown for budesonide in Example 1 on pages 27-28 appears to be much less than that indicated in Beckert's Figure 1 for what appears to be a representative active agent. However, the Examiner should compare the significantly increased release rates for

budesonide in Examples 2-3 on pages 28-30 of Applicant's Specification wherein budesonide is bound in a Eudragit® L 30 D-55, a copolymer with acid groups in accordance with Claim 2 (Spec., p. 7, ll. 18-22). The release rate for budesonide bound in a binder in accordance with Applicant's claimed invention is significantly greater than any release rate indicated by Beckert and entirely unexpected in view of Beckert's teaching as a whole.

Finally, the Examiner concludes that the formulation Applicant claims would have been prima facie obvious to a person having ordinary skill in the art in view of Beckert's disclosure as a whole, irrespective of the fact that Beckert does not disclose or reasonably suggest using any polymer or copolymer with acidic groups to bind budesonide at the core (OA, p. 6). The Examiner's conclusion is contrary to a wealth of controlling legal precedent. To establish the *prima facie* obviousness of the claimed subject matter, there must be some suggestion to do what Applicant has done. That suggestion can be found either in the applied references or in the knowledge generally available to persons having ordinary skill in the art. *In re Jones*, 958 F.2d 347, 351 (Fed. Cir. 1992); *In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1988). However, where there is no instruction, motivation, or incentive to make the chemical modifications necessary to arrive at the claimed subject matter, a prima facie case of obviousness has not been established. *See In re Grabiak*, 769 F.2d 729, 731-32 (Fed. Cir. 1985) ("[T]here must be adequate support in the prior art for the [prior art] ester/[claimed] thioester change in structure, in order to complete the PTO's *prima facie* case . . . ."); *In re Lalu*, 747 F.2d 703, 705 (Fed. Cir. 1984)("The prior art must provide one of ordinary skill in the art the motivation to make the proposed molecular modifications needed to arrive at the claimed compound."). In this case, the Examiner has not pointed to any teaching or suggestion, and has not provided any motivation, to use polymers or copolymers with acidic groups as a binder for the budesonide active agent at the core of Beckert's multilayer pharmaceutical product for any purpose. Moreover, the comparative evidence of record

surprisingly shows that Applicant's claimed formulation with an inner layer of budesonide bound in a polymeric or copolymeric binder with acidic groups is far superior in releasing budesonide to otherwise identical formulations with an inner layer of budesonide either unbound or bound to a representative polymeric binder without acidic groups such as sucrose. The collective evidence favoring patentability greatly outweighs the evidence to the contrary. Accordingly, the Examiner's final rejection of Claim 1 should be withdrawn.

We feel obliged remind the Examiner that the PTO has the initial burden of proof to establish the factual basis for its rejections under 35 U.S.C. 103. *In re Piasecki*, 745 F.2d 1468, 1472 (Fed. Cir. 1984). In that regard, Applicant notes that the Examiner has not explained why dependent Claims 3, 4, and 11 with their unique and distinct limitations would have been prima facie obvious in view of Beckert's deficient disclosure. Needless to say, previously presented Claims 3, 4, and 11 do not stand or fall with previously presented Claims 1, 2, 5-8, 10, and 12. The Examiner has not established that previously presented dependent Claims 3, 4, and 11 would have been prima facie obvious to a person having ordinary skill in the art in view of Beckert's teaching.

For the reason stated, Applicant's previously presented Claims 1-8 and 10-12 are patentable over the applied prior art and in condition for allowance. Early Notice of Allowance is respectfully requested.

Respectfully submitted,

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